https://doi.org/10.48047/AFJBS.6.12.2024.3868-3871

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Advances in treatment with Cannabidiol in Dravet Syndrome

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Article History
Volume 6, Issue 12, 2024
Received: 02 Jun 2024
Accepted: 25 Jun 2024
doi:
10.48047/AFJBS.6.12.2024.3868-3871

Abstract —

Introduction: *Epilepsy is a cause of disability and morbidity in children and adults. Dravet Syndrome (DS) is an epileptic encephalopathy that develops early in childhood, most often associated with a loss-of-function mutation in the SCN1A gene. Currently, around 30 anticonvulsants are available for use, most of which have been recently approved. Anticonvulsant therapy results in freedom from seizures in 70% of pediatric patients. The choice of treatment must be made by relating the patient's characteristics, side effects of the antiepileptic drug, social and socioeconomic factors. The difficulty in treating refractory epilepsies indicates the importance of developing new drugs.*

Objectives: *The research aims to evaluate publications on the efficiency of using cannabidiol associated with standard antiepileptic treatment in DS and the adverse effects of this intervention.*

Methods: *The research consists of a literature review carried out by searching for publications in the PubMed, Scielo and Cochrane Library databases between 2018 and 2024, with the keywords "Dravet syndrome" and "Dravet syndrome and treatment and cannabidiol". The inclusion criteria were original articles, systematic reviews, meta-analyses and double randomized clinical trials available free of charge in Portuguese, English or Spanish. Exclusion criteria were duplicate articles, articles that did not evaluate the use of cannabidiol associated with standard epilepsy treatment in Dravet syndrome.*

Results: *Among the 10 studies analyzed, all showed positive results regarding the standard treatment of epilepsy associated with cannabidiol, reducing the number and frequency of seizures in patients. The treatment showed acceptable safety, however, the incidence of adverse effects was sensitive. The adverse effects indicated in 100% of the studies were elevation of liver enzymes (mainly in patients who used sodium valproate associated with treatment) and drowsiness. Furthermore, the effects of decreased appetite (90%), diarrhea (70%), pyrexia (50%), vomiting (40%) and gastrointestinal discomfort (10%) were common.*

Conclusion: *The difficulty in treating epilepsy in patients with Dravet syndrome indicates the need for a combination of different drugs. Cannabidiol can be considered a safe and effective option to combine with treatment, as it reduces the number and frequency of epileptic seizures. However, it presents important adverse effects such as decreased appetite, drowsiness, diarrhea, pyrexia, vomiting and elevation of liver enzymes, which is more pronounced in patients who use sodium valproate associated with treatment. Therefore, the complexity of*

https://doi.org/10.48047/AFJBS.6.12.2024.3857-3867

the treatment and the scarcity of studies highlight the importance of more research to better evaluate adverse effects and drug interactions.

Index Terms — *Epilepsy* ; *Dravet syndrome* ; *Cannabidiol*

I. INTRODUCTION

Epilepsy is a cause of disability and morbidity in children and adults.[1] Dravet Syndrome (DS) is an epileptic encephalopathy that develops early in childhood, most often associated with a loss-of-function mutation in the SCN1A gene.[2] The SCN1A gene (type 1 voltage-dependent sodium channel alpha subunit) responsible for coding the expression of the alpha subunit (Na V 1.1), a protein present in a type 1 voltage-gated sodium channel, present in inhibitory neurons GABAergic, mainly in the hippocampus and cerebellum. This genetic error decreases the release of the neurotransmitter GABA by interneurons, impairing the disinhibition mechanism of the central nervous system.[3]

Currently, around 30 anticonvulsants are available for use, most of which have been recently approved. These drugs may be related to the modulation of voltage-dependent ion channels (including sodium and potassium channels), intensification of GABA-mediated inhibition (they may act on GABA receptors, GABA 1 transporters, GABA-synthesizing enzyme or GABA-metabolizing enzyme), modulation of synaptic release and inhibition of synaptic excitation mediated by ionotropic glutamate receptors.[4] Anticonvulsant therapy results in freedom from seizures in 70% of pediatric patients. The choice of treatment must be made by relating the patient's characteristics, side effects of the antiepileptic drug, social and socioeconomic factors. Furthermore, progressive reduction of the drug can be carried out at 2 years or more without seizures. This decrease is accomplished in 6 weeks or more.[5] Among the most important factors for choice are low risk of drowsiness and cognitive dullness. The mechanism of action is important in cases of treatment with different drugs. Furthermore, the number of doses required per day, rapid titration capacity and drug interactions with other drugs are analyzed when choosing treatment.[5]

Approximately one third of patients with epilepsy do not respond to pharmacological treatment with anticonvulsants.[1] When drug treatment with one or more antiepileptics is not effective, new treatment alternatives should be discussed.[5] Studies indicate that surgical treatment of drug-resistant epilepsy in children and adolescents leads to greater absence of seizures and improvement in patients' quality of life compared to drug treatment alone.[6] New forms of epilepsy treatment with dietary therapies, RNS (responsive neurostimulation) and DBS (deep brain stimulation) are important options for patients with refractory epilepsy.[1] The difficulty in treating refractory epilepsies indicates the importance of developing new drugs. In this sense, cannabidiol proves to be a good option, as it presents satisfactory results in crisis control. Also noteworthy is the uncertainty regarding long-term adverse effects, drug interactions and lack of regulation in the production of drugs with cannabidiol, indicating the need for more studies.[7]

II. OBJECTIVES

The research aims to evaluate publications on the efficiency of the use of cannabidiol associated with standard antiepileptic treatment in DS and the adverse effects of this intervention.

III. METHODS

The research consists of a literature review carried out by searching for publications in the PubMed, Scielo and Cochrane Library databases between 2018 and 2024, with the keywords “Dravet syndrome” and “Dravet syndrome and treatment and cannabidiol”. The inclusion criteria were original articles, systematic reviews, meta-analyses and double randomized clinical trials available free of charge in Portuguese, English or Spanish. Exclusion criteria were duplicate articles, articles that did not evaluate the use of cannabidiol associated with standard epilepsy treatment in Dravet syndrome.

IV. RESULTS

Among the 10 studies analyzed, all showed positive results regarding the standard epilepsy treatment associated with cannabidiol, reducing the number and frequency of seizures in patients. The treatment showed acceptable safety, however, the incidence of adverse effects was sensitive. The adverse

effects indicated in 100% of the studies were elevation of liver enzymes (mainly in patients who used sodium valproate associated with treatment) and drowsiness. Furthermore, the effects of decreased appetite (90%), diarrhea (70%), pyrexia (50%), vomiting (40%) and gastrointestinal discomfort (10%) were common.

Treatment with a highly purified solution based on cannabidiol oil can be used for different causes of epilepsy, showing a reduction in the frequency of seizures when compared to placebo. However, it presents adverse effects such as drowsiness, decreased appetite, diarrhea and increased serum aminotransferases.[8]

Randomized double-blind study with children aged 4 to 10 years administered cannabidiol at 5, 10 or 20 mg per kilogram per day associated with standard antiepileptic treatment (sodium valproate, levetiracetam and stiripentol). The most common adverse effects were pyrexia, drowsiness, decreased appetite, sedation, vomiting, ataxia and abnormal behavior. Furthermore, they observed an increase in liver enzymes in patients who used sodium valproate associated with treatment, but they did not meet the criteria for drug-induced liver injury and all recovered.[9]

Randomized double-blind study administering highly purified cannabidiol solution at 100 mg/mL, titrated from 2.5 to 20 mg per kilogram per day associated with standard antiepileptic treatment for two weeks concluded that long-term treatment with cannabidiol presents acceptable safety in patients with DS resistant to pharmacological treatment. This treatment option reduces the frequency of seizures and total seizures, with 80% of patients reporting an improvement in their general condition. The most common adverse effects were diarrhea, pyrexia, decreased appetite, drowsiness and vomiting. Furthermore, there was an increase in liver enzymes, especially in patients who used sodium valproate associated with the treatment.[10]

Treatment with cannabidiol is safe and reduces the frequency of seizures in patients with DS. The most common adverse effects are drowsiness, decreased appetite, diarrhea, vomiting and increased aminotransferases.[11]

Study carried out in children and adults with DS or Lennox-Gastaut syndrome, administered highly purified cannabidiol oral solution (Epidiolex 100 mg/mL) to 2 at 10 mg per kilogram per day associated with standard antiepileptic treatment concluded that the intervention reduced the frequency of seizures in patients and presented acceptable safety. However, they presented adverse effects, such as drowsiness, diarrhea, decreased appetite, fatigue, pyrexia, vomiting and changes in liver enzymes.[12]

DS treatment associated with cannabidiol shows a greater reduction in the frequency of seizures when compared to placebo. However, they presented adverse effects such as drowsiness, decreased appetite, diarrhea and increased liver enzymes.[13]

Cannabidiol reduces epilepsy seizures compared to placebo in patients with DS and Lennox-Gastaut syndrome. However, they presented adverse effects such as drowsiness and decreased appetite. Furthermore, they observed an increase in liver enzymes, especially in patients who used sodium valproate associated with the treatment.[14]

Purified high-grade cannabidiol oral solution represents an effective treatment option for patients with DS and Lennox-Gastaut syndrome. However, they present adverse effects such as drowsiness, gastrointestinal discomfort and increased serum liver enzymes. Furthermore, it has a drug interaction with clobazam.[15]

Randomized double-blind study administered a highly purified oral solution of cannabidiol at 100 mg/mL, titrated to 2.5 to 20 mg per kilogram per day associated with standard treatment for two weeks, concluded that long-term treatment with cannabidiol presents acceptable safety and results in a decrease in the frequency of seizures in patients with treatment-resistant DS. However, they present adverse effects such as diarrhea, pyrexia, decreased appetite and drowsiness, in addition to an increase in liver enzymes, especially in patients who used sodium valproate associated with the treatment.[16]

V. DISCUSSION

Among the articles analyzed, all presented positive results regarding the standard treatment of epilepsy associated with cannabidiol, reducing the number and frequency of seizures in patients. The treatment

showed acceptable safety, however, the incidence of adverse effects was sensitive. The adverse effects indicated in all articles were elevation of liver enzymes (mainly in patients who used sodium valproate associated with treatment) and drowsiness. Furthermore, they reported decreased appetite, diarrhea, pyrexia, vomiting, gastrointestinal discomfort and abnormal behavior.

Conclusion

The difficulty in treating epilepsy in patients with Dravet syndrome indicates the need for different drugs. Cannabidiol presents a safe and effective option, reducing the frequency of epileptic seizures, however, it has adverse effects such as decreased appetite, drowsiness, diarrhea, pyrexia, vomiting and elevated transaminases. The elevation of liver enzymes was more pronounced in patients using sodium valproate associated with the treatment, while depressant effects such as drowsiness were more related to patients using clobazan. Therefore, more studies are needed to better evaluate adverse effects and drug interactions.

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